

Vitamin C in Clinical Therapeutics

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Dear Sirs,

I read with great interest Dr. Shader's editorial that discussed vitamin C [1]. I share many of his concerns about methodological and statistical problems in the vitamin C trials. Nevertheless, some of my conclusions of the field are more positive.

Based on the currently published findings of randomized controlled trials (RCTs), there is no justification to encourage general populations of Western countries to take vitamin C regularly to prevent colds, cancers, or cardiovascular diseases [2,3].

Vitamin C, however, is a water-soluble antioxidant and it is possible that its administration may have effects on people who have elevated levels of oxidative stress in their body. Oxidative stress is increased, for example, by heavy exertion, infections and cardiac operations [4,5]. Furthermore, the level of vitamin C synthesis is increased by various forms of stress in those animals that synthesize their own vitamin C. By analogy, larger vitamin C intakes might be beneficial for humans when they are under some forms of stress, as humans are unable to synthesize their own vitamin C.

In 5 RCTs involving a total of 598 marathon runners, skiers and soldiers on subarctic exercises, vitamin C decreased the incidence of colds by 52% (95%CI 3665%) [2]. In one RCT, vitamin C shortened the duration of colds in adolescent male swimmers by 47% (95%CI 1480%), but had no effect on females [6]. In 3 RCTs with a total of 40 participants with exercise-induced bronchoconstriction (EIB), vitamin C reduced the post-exercise FEV₁ decline by 48% (95%CI 3364%) [7]. The participants of these 9 RCTs were under heavy physical stress and thus these findings cannot be extrapolated to sedentary people.

As to vitamin C and asthma, Dr. Shader wrote that I was "essentially taking a nonparametric view of cumulative data. Although [Hemilä] does not use an actual sign test, his implication is that the sheer number of positive, small sample reports prove his case." This statement is not correct as the above-mentioned 48% effect on EIB was calculated with a standard parametric meta-analysis approach [7]. I had indeed challenged the conclusions of the Cochrane review on vitamin C and asthma on statistical grounds since there were severe errors in the extraction of data and in the statistical analyses such as using the un-paired t-test for paired data [8,9].

Our Cochrane meta-analysis of over two dozen placebo-controlled trials calculated that ≥ 1 g/day vitamin C shortens the duration of colds in children by 18% (95%CI 927%) and in adults by 8% (95%CI 412%) [2,4]. Two RCTs found linear dose responses in the effect on cold duration by up to 6 and 8 g/day doses of vitamin C, with colds being shortened by some 20% on the higher dose [4]. Still higher therapeutic dosages might lead to greater benefits, but have not been investigated yet.

Dr. Shader criticized vitamin C and common cold trials for various reasons, yet I do not consider some of his comments valid, nor do I agree with several other comments. I do agree fully with Dr. Shader's description of the common cold being a heterogeneous pathological entity. However, that does not refute the benefits of vitamin C in the controlled trials mentioned above. If a trial investigates the effects of vitamin C on an experimental rhinovirus infection, it is not clear how far the results can be generalized to the common colds in the general population. However, the primary focus of our Cochrane review was on colds in the general population and therefore the findings seem relevant even though colds are heterogeneous [2]. Importantly, since the trials used concurrent controls, the variation in common cold incidence over years and seasons did not bias the comparisons. Finally, the vitamin C was ascorbic acid and the placebo was citric acid in most of the trials in the Cochrane review. Therefore, a placebo effect caused by taste difference in those studies is a debatable explanation for the differences between the vitamin C and placebo groups [2].

The reported clinical effects of vitamin C are not limited to the common cold and EIB. Fourteen RCTs examined the effects of vitamin C on post-operative AF (POAF) in cardiac surgery patients. Vitamin C had no effect on POAF in 5 trials carried out in the USA. However, vitamin C decreased the incidence of POAF on average by 44% (95%CI 3353%) in 9 trials conducted in Iran, Greece, Russia, and Slovenia [5]. In a cardioversion trial carried out in Greece, vitamin C decreased the risk of AF recurrence by 87% (95%CI 898%) [5]. Finally, one meta-analysis of patients with atherosclerosis or heart failure reported that vitamin C improved endothelial function [10], another meta-analysis revealed that vitamin C reduced blood pressure [11], and a third showed that vitamin C

decreased the risk of contrast-induced acute kidney injury in patients undergoing coronary angiography [12]. Thus, vitamin C may have therapeutic effects in certain special conditions, although regular vitamin C supplementation does not seem beneficial for ordinary people [2,3].

Vitamin C field is indeed complex and confusing. It is puzzling that the many positive RCTs on vitamin C have been largely ignored by mainstream medicine, which may be explained by a few historical factors [4]. For instance, the substance vitamin C was identified as the etiological explanation for scurvy, which was considered a disease of the connective tissues. It may have seemed irrational to consider that a substance that was assumed to participate ‘only’ in collagen metabolism might also have effects on infections, pulmonary functions, and cardiac disorders. However, the biochemistry of vitamin C is complex and not limited to collagen metabolism [4,5].

I do agree with Dr. Shader that more research on vitamin C is needed. On the other hand, published RCTs in general give us the average effect of a treatment, but there are individual variations around the average. As to the self-medication anecdote alluded to by Dr Shader, an analogy is the individual level experimentation that is usual practice in clinical therapeutics to figure out whether, say, a particular triptan is effective for a certain patient with migraine. The same reasoning goes for vitamin C. Vitamin C is an inexpensive essential nutrient and there is little evidence of adverse effects of high doses [13]. It seems reasonable, therefore, to encourage common cold patients to test for themselves whether vitamin C might benefit them at the individual level [2].

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